UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,801	12/16/2003	Bert Klebl	DEAV2002/0089 US NP	4154

5487 7590 06/23/2011

ANDREA Q. RYAN
SANOFI-AVENTIS U.S. LLC
1041 ROUTE 202-206
MAIL CODE: D303A
BRIDGEWATER, NJ 08807

EXAMINER	
HAMA, JOANNE	

ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
06/23/2011	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPatent.E-Filing@sanofi-aventis.com
andrea.ryan@sanofi-aventis.com

Office Action Summary	Application No.	Applicant(s)
	10/736,801	KLEBL ET AL.
	Examiner	Art Unit
	JOANNE HAMA	1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 April 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-36 and 38-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-36 and 38-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)	
1) ☒ Notice of References Cited (PTO-892)	4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)	5) ☐ Notice of Informal Patent Application
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.	6) ☐ Other: _____.

DETAILED ACTION

Applicant filed a response to the Non-Final Action of June 30, 2010 on December 16, 2010.

In the claims filed April 13, 2011, claims 1-23, 37 are cancelled.

Claims 24-36, 38-40 are pending.

Election/Restrictions

Applicant's election of "kinase" in claims 39, 40, in the reply filed on April 13, 2011 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 24-36, 38-40, drawn to a method for generating genetically modified yeast and to said yeast, are under consideration.

Withdrawn Rejection

35 USC 112, 2nd parag.

Applicant's arguments, see page 7 of Applicant's response, filed December 16, 2010, with respect to the rejection of claims 28, 29 have been fully considered and are persuasive. Applicant indicates that claim dependency of claim 28 has been amended. The rejection of claims 28, 29 has been withdrawn.

35 USC 102

Applicant's arguments, see pages 8-9 of Applicant's response, filed December 16, 2010, with respect to the rejection of claims 24, 30-34, 38 as being anticipated over Hartman et al., 2001 have been fully considered and are persuasive. Applicant indicates that Hartman et al. do not teach a foreign gene encoding a protein. The rejection of claims 24, 30-34, 38 has been withdrawn.

New/Maintained Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-36, 38-40 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Applicant indicates that claim 24 has been amended to indicate that the expression of the foreign gene does not produce any detectable change of any phenotype perceptible from the outside. The amendment indicates that not only a specific phenotype, such as over-proliferation or survival, is addressed and investigated, but that the sum of all phenotypes as they are perceptible is addressed (Applicant's emphasis, Applicant's response, page 12). It is noted that the Examiner has looked

through the specification for support for "any" phenotype to mean "all" phenotypes and could not find support. Further, the Examiner has not found support that the mutant yeast cannot exhibit "all" types of phenotypes, i.e. that the mutant yeast is the same as wild type yeast in all phenotypes.

Claim 29 is read such that the yeast comprises a conditional knockout of the compensating differentially regulated gene. The Examiner has looked through the specification for support for this limitation and could not find any. Thus, the claims are rejected for new matter.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended claim 35 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is unclear as it appears to be missing a word or words should be deleted. Applicant's response, page 7, under Remarks indicates that support for claim 35's amendment can be found through the specification, but particularly on page 4, lines 9-11. In looking at page 4, lines 9-11, the Examiner cannot determine what word was intended to be used in the amendment of claim 35. For purposes of compact prosecution, the Examiner has interpreted claim 35 to mean, "a genetically modified expression of at least one foreign gene, which is associated with compensating differential expression of at least one gene."

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24, 30, 31, 33, 34, 38 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423, previously cited, for reasons of record, April 10, 2007, January 4, 2008, August 12, 2008, March 19, 2009, December 11, 2009, June 30, 2010.

The rejection of April 10, 2007 is copied below for Applicant's convenience.

Chattopadhyay et al. teach that btn1 encodes a nonessential protein that is 39% identical and 59% similar to human Cln3p. Deletion of BTN1 had no effect on mitochondrial function or the degradation of mitochondrial ATP synthase subunit c (Chattopadhyay et al., 2nd col., 1st parag.). Chattopadhyay et al. teach that disruption in btn1 (btn1Δ) in yeast result in yeast that have an elevated activity of the plasma membrane H+-APTase. Microarray analysis showed that btn1Δ yeast compensate for the altered plasma membrane H+-ATPase activity by elevating the expression of two genes, HSP30 and BTN2 (Chattopadhyay et al., abstract).

With regard to Chattopadhyay et al.'s teaching of not exhibiting a change of phenotype, it is noted that the yeast do not exhibit any phenotype when grown of normal media, and thus, Chattopadhyay et al.'s yeast is readable on the claims. It is noted that the yeast exhibit a phenotype when grown in a particular condition (sorbic acid).

To clarify the rejection of claim 38, with regard to claim 38 being drawn to an assay for drug screening, Chattopadhyay et al. teach that hsp30, btn2 double knockout yeast were grown in the presence of sorbic acid and that the yeast had a growth defect greater than that of the single mutant yeast (Chattopadhyay et al., page 6420, 2nd col.).

Applicant's arguments filed December 16, 2010 have been fully considered but they are not persuasive.

Applicant indicates that the claims are directed to methods of generating a genetically modified yeast for drug screening and include a step of introducing a heterologous gene (Applicant's emphasis, Applicant's response, page 8). In response, this is not persuasive. As indicated in the Office Action, December 16, 2010, page 5, methods for making the yeast used by Chattopadhyay et al. is described in Pearce et al., 1997, Yeast, 13: 691-697, of record. Pearce et al. teach that the btn1-Δ was made by insertion of the His3 gene (Pearce et al., Figure 1).

As such, the claims remain rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-29, 32-36, 38 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423 previously cited, in view of Sauer, 1987, Molecular and Cellular Biology, 7: 2087-2096, previously cited, Hartman et al., 2001, Science, 291: 1001-1004, previously cited, for reasons of record, June 30, 2010.

It is noted that this rejection was of record June 30, 2010 and is copied below for Applicant's convenience. Upon further consideration, the rejection applies to the instant claims.

As discussed above, Chattopadhyay et al. teach a method of generating genetically modified yeast comprising the steps of disrupting BTN1, conducting a microarray study to determine that HSP30 and BTN2 were upregulated, and disrupting HSP30 and BTN2 expression in BTN1 null yeast.

However, Chattopadhyay et al. do not teach that the modified expression step is inducible.

At the time of filing, Sauer teach that the cre-lox site-specific recombination system was shown to function in an efficient manner in yeast. The cre gene, which codes for a site-specific recombinase, was placed under control of the yeast GAL1 promoter. lox sites flanking the LEU2 gene were integrated into two different chromosomes in both orientations. Excisive recombination at the lox sites (as measured by the loss of the LEU2 gene) was promoted efficiently by the Cre protein and was dependent upon induction by galactose (Sauer, abstract).

Therefore, it would have been obvious to take the cre-lox system taught by Sauer and to flank the endogenous BTN1 sequence with lox sites. An artisan would have done so in order to arrive at a yeast culture that can be split in half, wherein one half is induced with galactose. An artisan would then purify the mRNA from the galactose-induced and uninduced yeast and compared the mRNA expression between them in order to determine what genes were up- and downregulated following loss of BTN1 expression.

With regard to the claims being drawn to the genetic modification comprising introducing a vector which enable the at least one protein or protein fragment to be inducibly expressed (claim 26), it is noted that with regard to the limitation of "protein fragment" an artisan can design the loxP sites to excise almost the entire coding sequence of BTN1 such that only the 5' stump of BTN1 is expressed. With regard to the expression being inducible, it is noted that expression of the 5' stump of BTN occurs following induction of the cre-lox system.

With regard to claim 32 being drawn to the differentially expressed gene being less strongly expressed than in control organisms and the reduction or elimination of differential expression is carried out by enhancing expression of the differentially expressed gene, it is noted that while Chattopadhyay et al. focused on the two genes that were upregulated in BTN1

knockout yeast, an artisan would also have looked at genes that were downregulated in BTN1 knockout yeast in order to determine what effect(s) downregulated genes had on BTN1 knockout yeast. To do so, an artisan would have introduced a transgene construct overexpressing these downregulated genes. See for example, Hartman et al., 2000, who teach it would be desirable to study buffering relationships (Hartman et al., page 1004, 1st col., under Mechanisms of Buffering).

With regard to claim 35 being drawn to a genetically modified yeast that expresses at least one foreign gene that results in compensating differential expression of at least one other gene endogenous to the modified yeast organism, it is noted that cre recombinase is a foreign gene and that upon disruption of BTN1 via cre-lox excision, HSP30 and BTN2 are upregulated, as shown by Chattopadhyay et al., abstract.

With regard to the claims being drawn to a method of identifying a substance having an effect on the function of a heterologously expressed protein or protein fragment (claim 36), it is noted that when the artisan provides the yeast comprising loxP sites flanking a region in the endogenous BTN1 sequence with galactose, that galactose is the substance that has an effect on the function of a heterologously expressed protein and that an artisan can easily measure the change (i.e., the presence or absence) of BTN1 following loxP excision with methods known in the art (e.g. PCR).

To address the amendment of claims 28, 29, wherein the compensating differentially regulated gene is an inducible knockout, it is noted that an artisan would have also made conditional knockouts as taught by Sauer et al. for the compensating differentially regulated genes. As indicated above, an artisan would have made conditional knockout mutants in order to arrive at a convenient way of comparing knockout versus non-knockout yeast. More specifically for claims 28, 29, in making conditional knockouts of the compensating differentially regulated genes, an artisan would have made them so that one could compare the effect two mutations had on a yeast, versus one.

Applicant's arguments filed December 16, 2010 have been fully considered but they are not persuasive.

Applicant indicates that a decisive difference between Chattopadhyay and the instant invention is that the btn1 gene taught in Chattopadhyay is actively disrupted, whereas it is a requirement of the instant invention that a foreign gene is introduced into a yeast organism and that the influence of the foreign gene is investigated. (Applicant's response, page 10). In response, this is not persuasive. The rejection is Chattopadhyay et al. in view of Sauer et al. Chattopadhyay et al. teach a mutation in btn1, Sauer et al. teach that conditional knockout mutants are known in the art. As such, an artisan would have combined the teaching of Chattopadhyay et al. and Sauer et al. in order to arrive at conditional btn1 mutants. It is noted that Sauer et al. meets the limitation of "introducing a foreign gene" as Sauer et al. teach insertion of LEU2. With regard to Applicant indicating that the influence of the foreign gene is investigated, it is noted that the claims do not require this limitation. Claim 24 indicates that "the expression of the at least one protein or protein fragment does not produce any detectable change of any phenotype" refers to the "heterologous expression of at least one protein or protein fragment" that is modified by the foreign gene. In this case, the heterologous expression that reads on this limitation is btn1.

Applicant indicates that the difference between the combination of Chattopadhyay and Sauer suggested by the Examiner when compared to the instant invention is that the Cre gene does not directly induce modification of the expression of compensating differentially regulated genes. It is clear from the amended claims, if read

in light of the specification, that the expression of the heterologous genes in the yeast directly results in the modification of the expression pattern of the endogenous genes. In contrast to the scenario described by the Examiner, it is not envisaged by the amended claims that additional systems are present which result in the deletion of endogenous genes which in turn modify the expression patterns of other endogenous genes. The system proposed by the Examiner using Sauer requires the additional introduction of loxP sites allowing deletion of the sequence between loxP sites and such system is not comprised by the instant claimed set (Applicant's emphasis, Applicant's response, page 10). In response, this is not persuasive. With regard to Applicant indicating that the Cre gene does not directly induce modification of the expression of compensating differentially regulated genes, it is noted that the claims do not require "direct" modification of the expression of the compensating differentially regulated genes. With regard to amended claim 35, the amendment has been modified to be that the foreign gene is "associated with" compensating differential expression. However, "associated with" is not the same as "direct." With regard to Applicant indicating that if the claim is read in light of the specification, that the expression of the heterologous genes in yeast directly results in the modification of the expression pattern, it is noted that it is improper to import claim limitations from the specification. "Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment."

Superguide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). See also Liebel-Flarsheim Co. v. Medrad Inc., 358 F.3d 898, 906, 69 USPQ2d 1801, 1807 (Fed. Cir. 2004). See MPEP 2111.01. It is noted that in looking through the specification, there is no support for the foreign gene having a "direct" effect on the compensating genes' expression levels.

Applicant indicates that it is unambiguously clear that the introduction of a foreign gene into an organism directly influences the expression pattern of endogenous genes without requiring that additional systems be interposed. Applicant indicates that claim 24 has been amended to include the phrase, "associated with," and "and wherein the heterologous expression is associated with the alteration of the expression pattern of endogenous genes" as introduced into claim 24a. In the cited art, the expression of the foreign gene results in the deletion of an endogenous gene, however, only with the aid of an additionally introduced deletion system (Applicant's emphasis, Applicant's response, pages 10-11). In response, this is not persuasive. While one reading of claim 24 can be that overexpression of a foreign gene causes heterologous expression of at least one protein or protein fragment, it is noted that claim 24 can also be read such that the foreign gene (LEU2) can be inserted into a gene and cause a disruption in a gene of interest (btn1). That disruption is the "heterologous expression of at least one protein or protein fragment." In the instant case, the combination of references can also be applied to the second interpretation of the claims.

Thus, the claims remain rejected.

Claims 24-26, 30-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi et al., 2000, FEBS Letters, 470: 156-160, previously cited, Gari et al., 1997, Yeast, 13: 837-848, previously cited, Wilson et al., 1999, PNAS, USA, 96: 12833-12838, previously cited, for reasons of record, December 11, 2009, June 30, 2010.

The rejection of December 11, 2009 is copied below for Applicant's convenience.

DeRisi et al. teach that Pdr1p/Pdr3p transcription factors render the cell resistant to chemical and nutritional stress in several ways other than the well-known regulation of ABC efflux transporters. After overexpressing Pdr1p and/or Pdr3p in S. cerevisiae and identifying upregulated and downregulated genes, DeRisi et al. teach that many of the genes overexpressed by the PDR1-3 and PDR3-7 mutations encode proteins that reduce intracellular accumulation of hydrophobic compounds, modulate enzymes involved in lipid synthesis and cell wall metabolism. DeRisi et al. teach that it would be interesting to investigate whether similar strategies for defense against noxious chemical agents are employed by other microorganisms, such as pathogenic yeasts (DeRisi et al., abstract and page 159, 2nd col., 3rd parag.).

While DeRisi et al. do not specifically teach that the upregulated genes in yeast overexpressing Pdr1p and/or Pdr3p were knocked out or that the downregulated genes were overexpressed, it would have been obvious for an artisan to knockout the upregulated genes and overexpress the downregulated genes in Pdr1p, Pdr3p or Pdr1p/Pdr3p yeast, such that an artisan would eliminate yeast that are resistant to chemical and nutritional stress. An artisan would have carried out the method in S. cerevisiae and adapted the treatment to pathogenic yeast.

With regard to the claims being drawn to the yeast expressing a heterologous gene (claim 24), in the case where overexpression of Pdr1p, Pdr3p or Pdr1p/Pdr3p results in downregulation of a gene, that gene can be overexpressed under an inducible system to see what effect(s) gene overexpression has on yeast survival. At the time of filing, Gari et al. teach the tetracycline-regulatable promoter system, wherein tetracycline induces tetO-driven gene expression and induces expression of a gene of interest (Gari et al., page 838, 1st col., 3rd parag.). Time course studies of mRNA expression patterns following induction were known at the time of filing. For example, see Wilson et al., who teach changes in gene expression

following treatment with a drug. One would have made a Pdr1p, Pdr3p, or Pdr1/Pdr3p overexpression line, placed a gene of interest that is downregulated when Pdr1p, Pdr3p or Pdr1p/Pdr3p is overexpressed under the control of the tetracycline system, split the yeast in half and induced on half with tetracycline, in order to determine what effect(s) overexpression of the compensating gene has on yeast.

With regard to the claims being drawn to the yeast not exhibiting a detectable change in phenotype (claim 24), the yeast taught by DeRisi et al. do not have a detectable phenotype as the morphology of the yeast is unaffected. In addition to this, DeRisi et al. can be interpreted to exhibit no detectable phenotype on the behavior of the organism when the detectable phenotype is defined to be rate of proliferation. However, the rate of proliferation would be affected in Pdr1p and/or Pdr3p yeast that comprise a deletion in an upregulated gene or in yeast that comprise a construct overexpressing a downregulated gene as the upregulated genes are drawn to genes involved in drug resistance (DeRisi et al., page 158) and genes that are downregulated are drawn to genes involved in transport of acids (DeRisi et al., page 159), which would affect the homeostasis of the yeast.

With regard to the claims being drawn to using the yeast in screens (claims 36, 37), given that DeRisi et al. teach that overexpression of Pdr1p and/or Pdr3p results in drug-resistant yeast, an artisan would have wanted to use the yeast to screen for compounds that affect Pdr1p and/or Pdr3p, such that compounds can be identified to treat patients with pathogenic yeast.

Applicant's arguments filed December 16, 2010 have been fully considered but they are not persuasive.

Applicant indicates that DeRisi teaches yeast strains which show a detectable phenotype which clearly constitutes a difference compared to the present invention. Applicant reiterates that the present invention is directed to situations where expression of a foreign heterologous protein does not produce any detectable change of any phenotype that is perceptible (Applicant's emphasis, Applicant's response, page 12). In response, this is not persuasive. As indicated above, the phenotype exhibited by

DeRisi et al.'s yeast is drug resistance. As such, there is no phenotype, or modification of behavior and/or the morphology of the organism, which is perceptible from the outside for DeRisi et al.'s yeast.

Applicant indicates that DeRisi does not involve introducing foreign genes but instead deletes the endogenous Pdr genes. Applicant has amended claim 24 to further clarify and describe the invention by indicating that the expression of the foreign gene does not produce any detectable change of any phenotype, such as overproliferation or survival, and includes the sum of all phenotypes as they are perceptible (Applicant's emphasis, Applicant's response, page 12). In response, this is not persuasive. DeRisi et al.'s yeast were transfected with constructs comprising pdr1-3 or pdr3-7 transgenes (DeRisi et al., page 156, 2nd col. under Materials and Methods, 2.1 Strains and growth media) and thus meet the limitation of "foreign gene." Further, it is noted that DeRisi et al.'s yeast do not exhibit any phenotype, like that of wild type yeast, particularly when the yeast is grown in complete yeast media.

Applicant indicates that claims 35, 36 have been amended to more clearly describe the invention. In response, as indicated above, the amendment of claim 35 is unclear; for purposes of compact prosecution, the Examiner has interpreted the phrase to mean, "a genetically modified expression of at least one foreign gene, which is associated with compensating differential expression of at least one gene." In the instant case, overexpression of Pdr proteins is associated with the changes in gene expression that DiRisi et al. identified (see DiRisi et al., pages 157-159, Results). With

regard to the amendment of claim 36, DiRisi et al. meet the limitation of the claims as DiRisi et al. teach that the change in the behavior of their yeast is drug resistance.

Thus, the claims remain rejected.

Claims 24-26, 30, 31, 33-36, 39, 40 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Cliby et al., 1998, The EMBO Journal, 17: 159-169, Wright et al., 1998, Proc. Natl. Acad. Sci., USA, 95: 7445-7450, Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423, previously cited, Hartman et al., 2001, Science, 291: 1001-1004, previously cited.

Cliby et al. teach overexpression of ATR, a phosphatidylinositol kinase-related protein homologous to ataxia telangiectasia mutated (ATM), and a kinase-inactive allele of ATR (ATRkd) in human fibroblasts (Cliby et al., abstract). With regard to the claims being drawn to the cells not exhibiting any change in phenotype, it is noted that cells transfected with ATR have the same phenotype as cells that were not transfected with an ATR transgene construct (e.g. see Cliby et al., Figure 2, which illustrates that ATR expressing cells have the same biological response to DNA damaging agents as untransfected cells). It is also noted that ATRkd does not have a phenotype as their phenotype is seen after their cells are treated with DNA-damaging agents.

With regard to using yeast (claims 24, 30), it is noted an artisan would have used yeast because yeast have biological processes similar to that of mammals. For example, Wright et al. teach that human ATR in yeast can complement the UV

sensitivity of esr1-1 (MEC1) mutants in S. cerevisiae (Wright et al., page 7445, 2nd col., 1st parag.)

With regard to claim 24 being drawn to analyzing the modified gene expression and identifying compensating differentially regulated genes and phenotyping the yeast following the reduction or elimination of compensating differential expression, Chattopadhyay et al. teach that DNA microarray analysis can be used to identify genes that compensate for a mutation. Chattopadhyay et al. teach that a second mutation of removing the genes that compensated for btn1-/- survival was carried out (Chattopadhyay et al., abstract). Given this teaching, an artisan would have used a microarray to identify the genes that compensate for ATR overexpression. An artisan would then either reduce genes that were upregulated or increase expression of downregulated genes in yeast that overexpress ATR in order to identify the phenotype of ATR overexpression. Identifying the phenotype of ATR overexpression by changing the expression levels of the compensating gene would give an artisan insight into the biochemical pathways that ATR is involved in. See Hartman et al. who teach that biochemical pathways have been elucidated by identifying mutations in genes that either enhance or suppress the phenotype of a mutation in a known gene of that pathway (Hartman et al., page 1003, 1st col., 3rd parag.).

With regard to the claims being drawn to the expression being inducible (claim 25), Cliby et al. teach that ATR cDNA was expressed using the inducible tetracycline regulatory system (Cliby et al., page 160, 2nd col. under Doxycycline-inducible expression of wild-type and kinase-dead ATR in GM847 fibroblasts).

With regard to the claims being drawn to the reduction or elimination leading to growth inhibition (claim 33), Cliby et al. teach that ATR is involved in the cell cycle, thus indicating that the protein has a role in cell proliferation and growth.

With regard to the claims being drawn to identifying a substance having an effect on the function of a heterologously expressed protein or protein fragment (claim 36), it is noted that claim 24 does not specifically indicate that the yeast made by the process has one or two mutations. The step of phenotyping (step c) can be read such that the yeast of interest has one mutation and the phenotype was carried out to indicate that there is a relationship between the mutation in step a and the modified gene in step b. As such, Cliby et al.'s cells, comprising one mutation (i.e. an overexpression construct of ATRkr) is contacted with substances such as IR, and cis-platinum (Cliby et al., Figure 2) and its response compared with unmodified cells is that they are more sensitive to DNA-damaging compounds. Similarly, in contacting cells comprising ATR construct with DNA-damaging compounds, Cliby et al., Figure 2 show that these cells behave similarly to that of untransfected cells. It is noted that while the ATR transfected cells do not exhibit any phenotype different from that of cells with no construct, these cells meet the limitations of the claims because the method steps used on these cells is the same as those claimed.

Thus, the claims are rejected.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Wednesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Joanne Hama/
Primary Examiner
Art Unit 1632